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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,528	10/24/2003	Olaf Wilhelm	2923-576	7396

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EXAMINER

FEDOWITZ, MATTHEW L

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/691,528

Applicant(s)

WILHELM ET AL.

Examiner

Matthew L. Fedowitz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) ____ is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☒ Claim(s) 6 and 13 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/24/2003</u> | 6) <input type="checkbox"/> Other: ____ |

Objections

- A. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested:
“Novel Urokinase Inhibitors and Uses Thereof.”
- B. Claims 6 and 13 are objected to because the spelling of “5-fluoruracil” is incorrect. The correct spelling is “5-fluorouracil.” Claims 6 and 13 are also objected to because the claims as written state “and taxanes” or “and taxane,” respectively, thereby referring to taxane as a drug in itself. The term “taxane” in the pharmaceutical arts refers to a class of drugs called “taxanes.” Claims 5 and 13 should be written as “and a taxane.” Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

- 1) Determining the scope and contents of the prior art.
- 2) Ascertaining the differences between the prior art and the claims at issue.
- 3) Resolving the level of ordinary skill in the pertinent art.
- 4) Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over PENTAPHARM Product Catalog 1998, Xing *et al.* Cancer Research 57, 3585-3593 (1997), DeVita *et al.* (Cancer Principles & Practice of Oncology, Fifth Edition. Lippincott Williams & Wilkins 1997) and Medenica *et al.* (US 5,736,129)

A. Claim 1 is directed to a method for inhibiting the growth and/or spreading of malignant tumors, metastases and/or lung foci by administering the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier. Claim 2 further limits claim 1 and is directed to defining the tumor as one that affects lymphatic tissue. Claim 3 further limits claim 2 and is directed to defining the lymphatic tissue as lymph nodes. Claim 4 further limits claim 3 by defining the lymph nodes as axillary lymph nodes and intraperitoneal lymph nodes. Claim 5 further limits claim 1 by including the administration of a cytotoxic substance. Claim 6 further limits claim 5 by defining the cytotoxic substance as being elected from the group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-fluoruracil and taxane. Claim 7 further limits claim 6 by defining the taxane as paclitaxel. Claims 8 and 9 further limit claim 1 by defining the malignant tumors as breast cancer tumors and where the composition is administered once daily to once weekly.

Claim 16 is directed to a method of treating a malignant tumor by removing the tumor and administering the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically

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acceptable carrier. Claim 17 further limits claim 16 by including the administration of a cytotoxic substance and/or radiation therapy to said patient.

Xing *et al.* teach a method of preventing breast cancer growth, invasion and metastasis (see page 3585 introduction) to lungs and lymph nodes (see page 3589 first full paragraph) using a urokinase inhibitor in a pharmaceutically acceptable carrier continuously over the course of two weeks (see page 3586 third paragraph) and in combination cytotoxic substance (see page 3585 materials and methods).

Xing *et al.* does not teach the use of the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier. Xing *et al.* also does not teach that the cytotoxic substance should be selected from a group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-fluoruracil and taxane; where the taxane is paclitaxel. Nor does Xing *et al.* teach the surgical removal of a primary tumor and then the administration of the claimed compound alone or in combination with cytotoxic agents and/or radiation therapy.

As relating to claims 1-5, the 1998 PENTAPHARM Product Catalog teaches the hydrochloride salt of N α (2,4,6-Triisopropyl-phenylsulfonyl)-3-amidino-(L)-phenylalanine-4-ethoxycarbonyl-piperazide. The catalog also describes the compound in the following manner: "Pefabloc® uPA is a low molecular weight synthetic inhibitor for urokinase." It is well known in the pharmaceutical arts that a compound must be in the form of a weak acid in order for it to go into a pharmaceutical carrier solution; therefore, it is evident that PENTAPHARM (a company operating under a descriptive and suggestive name giving the impression of being a pharmaceutical manufacturer) manufactured the hydrochloride salt form prospectively

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considering its use as a pharmaceutical. Furthermore, DeVita *et al.* teach that it is well known in the art that carcinomas frequently spread and grow in the lymphatic system (see page 139 first full paragraph) and that the ultimate event that leads to mortality in breast cancer is metastasis (see page 1549 see first sentence under Angiogenesis and Metastasis). DeVita *et al.* also teach that investigations have focused on plasmin production where it is produced in the tumor area due to the action on plasminogen of secreted plasminogen activator urokinase (see page 1550 second full paragraph) and that metastasis of tumors depend on a balance between enzymes and their inhibitors (see page 1550 third full paragraph).

As relating to claims 6 and 7, Medenica *et al.* teach a method of treating cancer by the use of multi-chemotherapeutic drug regimen. (see abstract) that makes use of cisplatin (see column 16 lines 8-15), carboplatin (see column 9 lines 65-67), doxorubicin (see column 8 lines 39-45), epirubicin (see column 22 line 28), 5-fluorouracil (see column 17 lines 11-16) and paclitaxel (see column 10 lines 24-29)

As relating to claim 16 and 17, it is well known in the art that a common course of treatment of malignant tumors would include the surgical excision of a primary tumor from a patient followed by treatment with a cytotoxic agent and/or radiation therapy

Therefore, it would have been obvious to one having ordinary skill in this art at the time the invention was made and having the above cited references before him to obtain a method for inhibiting the growth and/or spreading of malignant tumors, metastases and/or lung foci by administering the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier; where the tumor is one that affects lymphatic tissue; where the lymphatic

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tissue is defined as lymph nodes; where the lymph nodes are axillary lymph nodes and intraperitoneal lymph nodes; where claim 1 is combined with the administration of a cytotoxic substance; where the cytotoxic substance as being elected from the group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-fluorouracil and taxane and where the taxane is paclitaxel. And, additionally, where the malignant tumors are breast cancer tumors and where the composition is administered once daily to once weekly.

Xing *et al.* provides the motivation for a new method for inhibiting the growth and/or spreading of malignant tumors, metastases and lung foci by the statement that “because the uPA/uPAR system plays a key role in tumor invasion and metastasis, inhibition of cell surface uPA activity is an attractive therapeutic target for controlling cellular invasiveness in cancer (see page 3585 second column second full paragraph).

B. Claim 10 is directed to a pharmaceutical composition comprising the L enantiomer of $N\alpha(2,4,6\text{-Triisopropylphenylsulfonyl})\text{-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide}$ as itself or as a salt in a pharmaceutically acceptable carrier as well as an additional pharmacologically active substance. Claim 11 further limits claim 10 and is directed to defining the other pharmacologically active substance as radio labels or cytotoxic substances. Claim 12 further limits claim 11 by narrowing the pharmacologically active substance to a cytotoxic substance. Claim 13 further limits claim 12 by defining the cytotoxic substance as selected from a group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-fluorouracil and a taxane. Claim 14 further limits claim 13 and define the taxane as paclitaxel.

Claim 15 is directed to a kit comprising separate containers where one contains the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt and the other contains radio labels and/or cytotoxic substances.

The teachings of Xing *et al.* are considered above. Xing *et al.* does not teach the use of the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier. Xing *et al.* also does not teach that the cytotoxic substance should be selected from a group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-fluoruracil and taxane; where the taxane is paclitaxel. Xing *et al.* also does not teach a kit comprising the claimed composition with and radio labels or cytotoxic substances

As relating to claims 10-15, the 1998 PENTAPHARM Product Catalog teaches the hydrochloride salt of N α (2,4,6-Triisopropyl-phenylsulfonyl)-3-amidino-(L)-phenylalanine-4-ethoxycarbonyl-piperazide. The catalog also describes the compound in the following manner: "Pefabloc® uPA is a low molecular weight synthetic inhibitor for urokinase." Moreover, it is well known in the pharmaceutical arts that a compound must be in the form of a weak acid in order for it to go into a pharmaceutical carrier solution.

Therefore, it would have been obvious to one having ordinary skill in this art at the time the invention was made and having the above cited references before him to obtain a pharmaceutical composition comprising the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier as well as an additional pharmacologically

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active substance; where the pharmacologically active substance is selected from group of radio labels or cytotoxic substances; where the pharmacologically active substance is narrowed to a cytotoxic substance; where the cytotoxic substance is selected from the group consisting of cisplatin, carboplatin, doxorubicin, epirubicin, 5-FU and a taxane and where the taxane is paclitaxel. Moreover, it would have been obvious to one having ordinary skill in this art at the time the invention was made and having the above-cited references before him to obtain a kit containing the above-mentioned contents because of the complementary use of the compositions.

Xing *et al.* provides the motivation for a pharmaceutical composition or a kit comprising the L enantiomer of N α (2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)phenylalanine-4-ethoxycarbonylpiperazide as itself or as a salt in a pharmaceutically acceptable carrier as well as an additional pharmacologically active substance. This is because Xing *et al.* specifically state that “the efficacy of currently available therapies for breast cancer is restricted by the disseminated nature of the disease, which is characterized by the progression of the majority of tumors to a phenotype that is resistant to both cytotoxic and hormonal therapies” and “therefore, the development of a complementary approach ... is required” (see pp. 3589-3590 first paragraph of discussion).

Conclusion

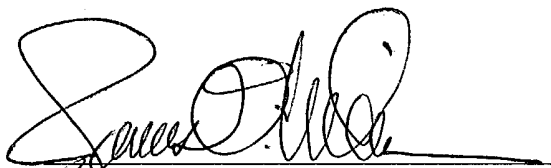
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-3105. The examiner can normally be reached on 9am-5:30pm (EST) M-F.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
November 12, 2004



James O. Wilson
Supervisory Patent Examiner
Art Unit 1623